JOSEPH F. BORZELLECA

Professor Emeritus
Pharmacology & Toxicology
Medical College of Virginia

President
Toxicology and Pharmacology, Inc.
Consultative Services

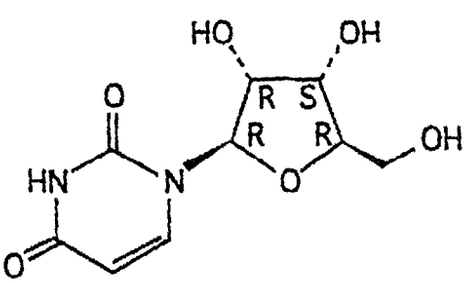
8718 September Drive, Richmond, VA 23229-7319 U.S.A.

Tele: 804.285.2004 Fax: 804.285.1401 Email: toxpro@aol.com

# A Critical Evaluation of the Available Information on the Toxicity/Safety of Orally Administered Uridine

The available safety information on orally administered Uridine is very limited. A comprehensive search of the Scientific Literature conducted by Dr. George A. Burdock failed to identify significant toxicity studies. The literature search, information provided by Dr. Lutz Thomas which included information on the characterization of uridine, manufacturing process, specifications and batch analyses, pharmacological effects, clinical studies and safety information (from Polifarma), and other materials deemed appropriate were critically evaluated to assess the safety of Uridine as a dietary supplement.

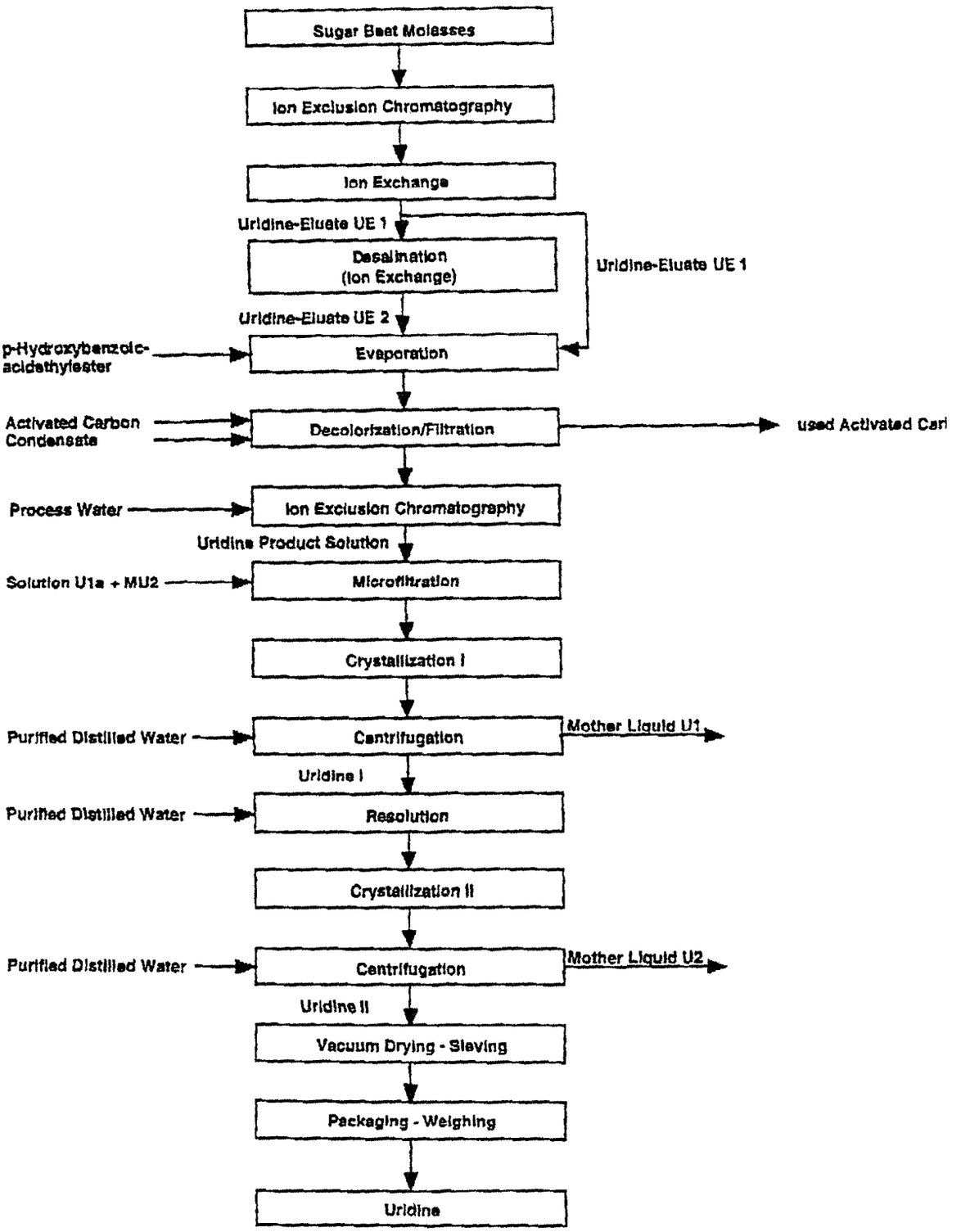
Uridine, 1-beta-D-ribofuranosyl-2, 4(1H, 3H)-pyrimidinedione, 1-beta-D-ribofuranosyl-uracil, 1-beta-D-ribofuranosyluracil (CAS Registry Number: 58-96-8 and E.C. number: 200-407-5) and with an empirical formula, C9 H12 N2 O6 and a structural formula,




is a nucleoside that is widely distributed in nature.

It is synthesized in the body and is involved in a number of biochemical reactions. For example, it is phosphorylated to form UMP (uridine monophosphate) and UDP (uridine diphosphate) which is then ultimately incorporated into DNA or it may be further phosphorylated to form UTP (uridine triphosphate) which may be synthesized into RNA or it may be involved in protein glycosylation or cellular membrane formation. Uridine is metabolized to uracil, which enters the tricarboxylic acid cycle by way of beta-alanine formation.

The following process using current Good Manufacturing Practice manufactures uridine.



The specifications for Uridine include the following:

| Parameter | Limit |
|---|---|
| Appearance:<br>White or almost white, crystalline powder | Passes |
| Identification | Passes |
| Transmittance (1% (m/V) in $H_2O$) | > 98.0% |
| Test on turbidity (10% (m/V) in $H_2O$) | ≤ Ref. Sups. I |
| Test on color (10% (m/V) in $H_2O$) | ≤ $BG_6$ |
| Chlorides | ≤ 200 ppm |
| Sulfates | ≤ 300 ppm |
| Ammonium | ≤ 200 ppm |
| Iron | ≤ 10 ppm |
| Heavy metals (as Pb) | ≤ 10 ppm |
| Loss on drying | ≤ 0.5% |
| Residue on ignition | ≤ 0.1% |
| Assay | 98.5 to 101.0% |
| Total viable aerobic count | ≤ 1000 CFU/g |
| Molds and yeasts | ≤ 100 CFU/g |
| Escherichia coli | in 1 g n.n. |
| Salmonella species | in 1 g n.n. |
| Pseudomonas aeruginosa | in 1 g n.n. |
| Staphylococcus aureus | in 1 g n.n. |

The following batch analyses confirm the consistency of Uridine manufactured by the process described above.

| Lot | 721000010 | 721000020 | 721000030 |
|---|---|---|---|
| Description | White or almost white crystalline powder | White or almost white crystalline powder | White or almost white crystalline powder |
| Identity | Passes | Passes | Passes |
| Test on turbidity | Passes | Passes | Passes |
| Test on turbidity | Passes | Passes | Passes |
| Chloride (Cl) | Not more than 200 ppm | Not more than 200 ppm | Not more than 200 ppm |
| Ammonia ($NH_4$) | Not more than 200 ppm | Not more than 200 ppm | Not more than 200 ppm |
| Sulfate ($SO_4$) | Not more than 300 ppm | Not more than 300 ppm | Not more than 300 ppm |
| Iron (Fe) | Not more than 10 ppm | Not more than 10 ppm | Not more than 10 ppm |
| Heavy metals (as Pb) | Not more than 10 ppm | Not more than 10 ppm | Not more than 10 ppm |
| Loss on drying | 0.03% | 0.02% | 0.04% |
| Residue on ignition | 0.03% | 0.03% | 0.04% |
| Assay (HPLC) | 100.5% | 99.8% | 100.2% |
| Total microbial count | Not more than 1000 CFU/g | Not more than 1000 CFU/g | Not more than 1000 CFU/g |

Some reported clinical indications and recommended doses include anti-arthritic, 1-5 mg/day; analgesic, 1.25-5.0 mg/day; neuropathies and polyneuropathies, 9-900 mg/day; CNS depression (sedative, anti-epileptic, neurological disorders, dysfunctional dopaminergic disorders); neurodegenerative disorders (for example, dementia, Parkinsonism, MS, ALS), 10 mg to 10 grams; following FU therapy, 1-12 g/$m^2$ [~24 grams], i.v. /day; orotic aciduria, 200 mg/day.

The acute oral toxicity of Uridine is extremely low, $LD_{50}$ >10 g/kg in mice and rats (Petersone, I. et al, 1987); Politi, V. (2002) reported acute oral $LD_{50}$ > 4 g/kg in mice and rats. There were no consistent compound-related dose-dependent adverse effects reported in the following oral toxicity studies: 30-day repeated dosing study in rats at doses of 166 or 500 mg/kg bw/day; 30-

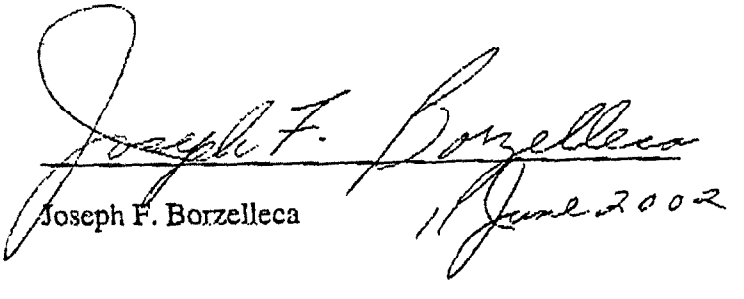
day repeated dosing study in rabbits at doses of 104 or 208 mg/kg bw/day; 120-day study in rats at doses of 83 to 250 mg/kg bw/day; 120-day repeated dosing study in dogs at doses of 104 to 250 mg/kg bw/day (Politi, V. 2002). There were no reported adverse effects on fertility, embryo genesis and peri-post natal development in rats and rabbits at oral doses of 50 to 416 mg/kg bw/day (Politi, V., 2002).

There are a number of human studies involving Uridine administration after 5-FU. Uridine was also investigated in healthy volunteers (Politi, V. 2002). For example, in the study by van Groeningen, et al (1991), Uridine was orally administered to six healthy volunteers and nine patients with metastatic colorectal cancer. It was reported "Oral Uridine was studied as single-dose administrations at doses escalating from 0.3 to 12 $g/m^2$ and as multiple-dose administrations every 6 hours for 3 days at doses from 5 to 10 $g/m^2$. The maximum tolerated dose was 10-12 $g/m^2$ for a single dose of Uridine and 5 $g/m^2$ (approximately 10 grams per day) for the multiple-dose regimen. Diarrhea was the dose-limiting toxic effect." [The total body surface for an adult male is 1.94 $m^2$ and for an adult female, 1.69 $m^2$, U.S. E.P.A., 1989]. In his critical evaluation of the available information, published and unpublished, on Uridine, Politi (2002) concluded that "Uridine is a rather safe drug in humans at least at doses up to 10 grams: side effects over this limit appear as fever and shivering [presumably due to the accumulation of beta-alanine, a metabolite of uracil which is a metabolite of Uridine] (by i.v. injection), and as diarrhea (by oral route)." He further notes "Uridine has been used for more than 30 years in Italy on several hundred thousand people, at doses up to 300 mg/day for several months, without reports of side effects. Moreover, small groups of children affected by Orotic aciduria are treated daily with very high doses of Uridine (200 mg/kg) for many years, without evidence of toxic effects."

It may be concluded from the above that the oral toxicity of Uridine is extremely low. For example, dogs tolerated doses of 250-mg/kg bw/day for 120 days, there was no evidence of reproductive or developmental toxicity at doses up to 416-mg/kg bw/day, and it was not genotoxic. The only side effect reported in humans was diarrhea at daily oral doses greater than approximately 10 grams/day. This is a self-limiting side effect. It may be further concluded that Uridine, at suggested daily doses of up to two grams per day as a dietary supplement, should not elicit adverse health effects.

Uridine at suggested daily doses of up to two grams/day as a dietary supplement should be safe for children and adults.

It is concluded from a critical evaluation of available information that Uridine at daily doses up to two grams should not elicit adverse health effects.



Joseph F. Borzelleca 1 June 2002

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